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Hospital-acquired pneumonia: Past, present, and perspectives

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ABSTRACT

Hospital-acquired pneumonia (HAP) remains the most frequent and lethal hospital acquired infection, driving ICU mortality, prolonged length of stay, and resource use. Ventilator-associated pneumonia (VAP), the archetypal form of HAP, has long defined both the risks and unintended costs of intensive care. Historically, management was shaped by timelines, culture-based diagnostics, and the central role of the endotracheal tube as both lifesaving and pathogenic. This paradigm promoted rigid definitions and empiric antibiotic strategies but also generated enduring lessons on airway care, aspiration, and biofilm biology.

Contemporary perspectives have shifted toward ecology and host response. The binary early–late VAP model has been replaced by a continuum of ventilatorassociated lower respiratory tract infections (VA-LRTI), from ventilator-associated tracheobronchitis to VAP. Colonisation, biofilm formation, and microbial–host interactions are now recognised as dynamic drivers of infection. Novel diagnostics—including multiplex PCR and next-generation sequencing—offer rapid pathogen and resistance detection, while biomarkers such as procalcitonin support stewardship and shorter antibiotic courses. Recognition of ventilated HAP (VHAP) has blurred traditional boundaries.

Looking forward, precision diagnostics, immune monitoring, and artificial intelligence promise to integrate ecology and immunity into personalised management. The future of HAP care lies not in faster antibiotics, but in tailored, ecology-informed, host-guided strategies that improve outcomes and preserve resilience in the critically ill.

1. Introduction

Hospital-acquired pneumonia (HAP) remains a defining challenge of modern intensive care. It is not only the most frequent hospital-acquired infection, but also one of the most lethal, driving mortality, prolonging ICU stay, and consuming healthcare resources. Within the ICU, ventilator-associated pneumonia (VAP) has become the emblematic form of HAP, symbolising both the achievements and the unintended costs of advanced life-sustaining technologies [1].

From the earliest days of intensive care, pneumonia has shaped daily practice, steered microbiology, and inspired prevention strategies. It forced clinicians to confront the difficult boundary between colonisation and true infection, a distinction that spurred diagnostic innovation and laid the groundwork for antimicrobial stewardship. At the same time, HAP has influenced the organization of ICUs themselves, serving as a marker of quality, a driver of infection control, and a catalyst for surveillance systems and bundle development [2].

This review follows the evolution of HAP across three stages: the past, dominated by timelines and culture-based definitions; the present, reshaped by ecology, immunity, and risk context; and the future, where precision diagnostics, immune monitoring, and artificial intelligence promise to redefine not only how we diagnose pneumonia, but how we prevent and treat it (Table 1).

Abbreviations: MDR, Multidrug Resistant; VAT, Ventilator-Associated Tracheobronchitis; VAP, Ventilator-Associated Pneumonia; VA-LRTI, Ventilator-Associated Lower Respiratory Tract Infection; ETA, Endotracheal Aspirate; BAL, Bronchoalveolar Lavage; NGS, Next-Generation Sequencing; VHAP, Ventilated Hospital-Acquired Pneumonia; HAP, Hospital-Acquired Pneumonia.

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Table 1
Practical takeaways for pneumonia management integrating Past, Present, and future Perspectives.

Domain	Key Message
Empiric therapy	Use risk-based prediction of MDR organisms rather than timing of intubation.
VAT and VAP	Consider them as a continuum under VA-LRTI. Treat clinically significant VAT when there is systemic impact to prevent progression.
Diagnostics	Use ETA for surveillance and BAL when greater specificity is needed. Consider NGS in culture-negative high-risk cases.
Candida	Do not treat Candida in respiratory samples unless invasive disease is suspected. Recognize its role as a colonizer and ecological influencer.
Biomarkers	Apply to support de-escalation and shorter courses, focusing on trends.
VHAP	Recognize ventilated HAP as high risk, with mortality similar to or greater than VAP.
Prevention	Prioritize microaspiration control, early mobilization, ventilator weaning, and microbiome stewardship.

2. The past: timelines, tubes, and the microbial chase

For decades, clinicians approached VAP primarily through the lens of time. "Early" episodes, within the first five days of intubation, were thought to arise from community-type organisms, whereas "late" episodes, after a week or more, were attributed to multidrug-resistant hospital flora. This simple dichotomy shaped empirical therapy, structured guidelines, and even informed quality reporting [3].

At the centre of this paradigm was the endotracheal tube: a lifesaving device, but also a prime instigator of infection. It disrupted natural defences, promoted microaspiration, and provided a surface for biofilm formation. Prevention strategies such as head-of-bed elevation, cuff pressure control, subglottic suctioning, and reduced sedation were all designed to mitigate these risks [4].

Diagnostics in this era were entirely culture-based. The endotracheal aspirate, valued for its simplicity, was most often used, while bronchoalveolar lavage was reserved for complex cases, offering greater specificity at the expense of invasiveness. This reliance on microbiology reinforced a rigid separation between HAP and VAP, as though mechanical ventilation itself defined a distinct disease [5].

For vulnerable patients, the outlook was grim. In transplant recipients, those with haematologic malignancies, or patients receiving high-dose corticosteroids, HAP and VAP often carried a near-uniformly fatal prognosis [6]. Respiratory *Candida* spp. was frequently misinterpreted as a pathogen [7], leading to unnecessary antifungal therapy, while cytomegalovirus (CMV) reactivation in critically ill or immunosuppressed patients was poorly understood, overlooked until late, and treated empirically without clear guidance [8].

Yet despite these limitations, enduring lessons emerged. Optimal airway care reduced infection risk, biofilm and aspiration were recognised as central to pathogenesis, and timely administration of appropriate antibiotics improved survival. These insights laid the groundwork for the more nuanced and ecology-driven approaches that followed.

3. The present: from the clock to ecology and the host

In the last two decades, understanding of HAP has shifted profoundly. The simplistic "early versus late" paradigm has been replaced by a focus on ecology and risk context. Today, clinicians consider prior antibiotic exposures, known colonisation with resistant organisms, length of hospitalisation, and unit-level prevalence when deciding empiric therapy; time alone is no longer decisive. This evolving complexity underscores the necessity of new guidelines for HAP and VAP, as emerging evidence suggests that conventional approaches may inadvertently cause harm. Increased mortality has been observed in patients at high baseline risk who received empirically two or more antibiotics, highlighting that "more antibiotics" is not always better [9] and may, in fact, be harmful. Moreover, the novel recognition that anti-anaerobic therapy suppresses protective anaerobic flora and may increase mortality further challenges traditional prescribing practices [10].

These insights parallel a deeper ecological understanding of the airway. The lower respiratory tract is not sterile but hosts low-biomass microbial communities maintained by immune surveillance. Hospitalisation, antibiotics, acid suppression, and intubation disturb this balance, favouring opportunistic pathogens. Colonisation is now seen as dynamic, with clinical meaning determined by microbial burden, biofilm formation, and host response. Viral dynamics further complicate this ecology: Herpes Simplex Virus (HSV) reactivation has been recognised as a contributor to difficult-to-treat pneumonia in the ICU [11], and the broader respiratory virome is increasingly acknowledged as a factor in HAP, despite having been largely overlooked in previous years [12].

Conceptually, ventilator-associated infections are now understood along a continuum of ventilator-associated lower respiratory tract infections (VA-LRTI) [13]. Ventilator-associated tracheobronchitis (VAT) represents infection confined to the tracheobronchial tree, while VAP reflects extension into the alveoli, with radiographic infiltrates and systemic effects [14]. Whether a patient halts at VAT or progresses to VAP depends on microbial pressure and the robustness of host defences. This continuum highlights infection as a trajectory rather than a binary event.

Diagnostics have also expanded. Endotracheal aspirates remain widely used, but bronchoalveolar lavage is increasingly applied when diagnostic certainty could alter therapy. Next-generation sequencing has emerged as a powerful adjunct, able to identify fastidious organisms and resistance genes missed by cultures. For rapid biomolecular diagnosis, systematic reviews of multiplex PCR panels show high accuracy, with a pooled sensitivity of 94 % and specificity of 98 % for respiratory bacterial pathogens [15] However, their clinical impact remains debated: a multicenter evaluation of PCR in respiratory samples of critically ill patients with hospital-acquired pneumonia found no improvement in outcomes, partly due to low adherence to stewardship recommendations, and although no data to date have shown a direct effect on prognosis, clinical trials have demonstrated a reduction in time with inadequate antibiotic therapy and facilitated de-escalation of antibiotics targeting Gram-positive bacteria [16,17]. Interpretation, therefore, remains complex, underscoring the need for integration into stewardship frameworks.

The management of immunocompromised patients illustrates how far the field has progressed. Once a near-fatal diagnosis, HAP and VAP outcomes in these groups have improved thanks to prophylaxis, targeted antiviral and antifungal strategies, and more refined risk stratification. CMV, now recognised as a contributor to morbidity, is monitored proactively with molecular assays, enabling earlier intervention [6].

The distinction between HAP and VAP has shifted over time. Initially, HAP was viewed as a separate entity from VAP, with ventilator-associated infection considered a distinct syndrome. Over the years, VAP has increasingly been conceptualised as a subset of HAP, essentially pneumonia that develops in hospitalised patients once they require mechanical ventilation. Ventilated hospital-acquired pneumonia (VHAP) illustrates this overlap, since patients with HAP who deteriorate and undergo intubation often fare as poorly, or even worse, than those with VAP at onset. This historical evolution has contributed to the current recognition that unified prevention and treatment strategies are needed across what were once seen as separate categories. [1].

At the same time, biomarkers have become valuable supportive tools in practice. While no single marker can establish a diagnosis of VAP, trends in C-reactive protein, procalcitonin, and host-response signatures provide crucial context. They now inform not only the decision to initiate or withhold antibiotics, but also the increasingly important goal of shortening treatment duration, aligning clinical care with the broader

movement toward precision medicine. Most recently, robust hospital-acquired pneumonia subphenotypes have been identified and validated across large multicohort datasets. These subphenotypes show distinct associations with systemic inflammation, respiratory microbiome dysbiosis, and mortality, as well as differential responses to therapy [18]. They offer a framework for prognostic enrichment and hold promise for guiding personalised treatment strategies in the future.

4. Perspectives: the road ahead

Looking forward, hospital-acquired pneumonia management is set to be transformed by precision diagnostics and immune-informed care. Artificial intelligence (AI) will integrate clinical data, ventilator waveforms, imaging, cultures, molecular panels, and immune signatures into unified probability models, shifting focus from pathogen isolation to state-based diagnoses that capture the interplay of ecology and immunity [19].

Bedside immune monitoring is likely to become routine. Rapid assays of monocyte HLA-DR expression, cytokine release capacity, or transcriptomic panels could stratify patients into hyperinflammatory or immunoparalysed states, guiding not only the duration of antibiotic therapy but also the timing of immune-targeted interventions [20].

Immune adjuvants represent an emerging frontier. Strategies such as granulocyte–macrophage colony-stimulating factor to restore monocyte function, interferons to counter immune paralysis, and bacteriophage therapy to disrupt biofilm-associated multidrug-resistant bacteria illustrate how treatment may evolve from pathogen-directed to host–pathogen rebalancing [21].

Future directions in HAP/VAP management must confront several parallel challenges and opportunities. The evolution of bacterial resistance, particularly among difficult-to-treat Gram-negative pathogens, remains a major global concern as the spread of resistance continues to outpace the limited development of new antibiotics. At the same time, treatment strategies are moving toward shorter and more adaptive courses, guided by biomarkers, clinical improvement, and microbiological results, to reduce unnecessary exposure without compromising safety. Beyond systemic antibiotics, alternative or complementary approaches such as inhaled antibiotics and phage therapy represent modalities that are simultaneously part of the past, present, and possibly the future of VAP treatment. Finally, there is likely a growing role for artificial intelligence, not only in refining diagnosis but also in tailoring therapy and supporting a transition from broadly defined recommendations to more personalised, patient-centred guidance. [22,23].

Finally, prevention strategies will expand beyond the ventilator bundle. Ecological engineering, from subglottic suction and biofilm-resistant endotracheal tubes to stewardship practices that preserve the airway microbiome, will be critical. Protecting microbial balance may ultimately prove as important as eradicating pathogens [24].

5. Conclusion

Hospital-acquired pneumonia remains one of the defining infections of critical care. Its trajectory mirrors the evolution of intensive care itself: the past dominated by timelines and cultures; the present shaped by ecology, immunity, and risk context; and the future poised to be transformed by precision diagnostics, immune-guided therapy, and ecological prevention. The challenge ahead is no longer to simply give antibiotics faster, but to deliver the right treatment to the right patient for the right duration. By integrating ecology, immunity, and time, HAP management can move from a reactive chase of pathogens to a proactive, personalised strategy, one that not only improves survival but also preserves resilience in the critically ill.

CRediT authorship contribution statement

Ignacio Martin-Loeches: Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Antoni Torres:** Writing – review & editing, Validation, Supervision, Conceptualization. **Antoine Roquilly:** Writing – review & editing, Validation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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